

University of Dundee

## Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Flatters, S. J. L.; Dougherty, P. M.; Colvin, L. A.

*Published in:*  
British Journal of Anaesthesia

*DOI:*  
[10.1093/bja/aex229](https://doi.org/10.1093/bja/aex229)

*Publication date:*  
2017

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

Flatters, S. J. L., Dougherty, P. M., & Colvin, L. A. (2017). Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. *British Journal of Anaesthesia*, 119(4), 737-749. <https://doi.org/10.1093/bja/aex229>

### **General rights**

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

# **Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A review**

Sarah J.L. Flatters <sup>1\*</sup>, Patrick M. Dougherty <sup>2</sup>, Lesley A. Colvin <sup>3</sup>

<sup>1</sup> Wolfson Centre for Age-Related Diseases, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE1 1UL, UK.

\* Corresponding author. Email: [sarah.flatters@kcl.ac.uk](mailto:sarah.flatters@kcl.ac.uk). Webpage: [www.kcl.ac.uk/flatterslab](http://www.kcl.ac.uk/flatterslab)

<sup>2</sup> The Department of Pain Medicine Research, The Division of Anesthesia, Critical Care and Pain Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA.

<sup>3</sup>. Dept of Anaesthesia, Critical Care & Pain Medicine, University of Edinburgh, Western General Hospital, Crewe Rd, Edinburgh, EH4 2XU, UK

**Short running title:** A review of chemotherapy-induced neuropathic pain

Word count: 5839 (excluding references, summary & figure legends) plus 2 tables, 1 figure

**Keywords:** neuralgia; paclitaxel; cancer pain

## **Author Contributions:**

SJLF: contribution to conception and design of review; co-wrote review article; final approval of the version to be published.

PAD: contribution to conception and design of review; co-wrote review article; final approval of the version to be published.

LAC: contribution to conception and design of review; drafting the article with co-authors; final approval of the version to be published;

## **Summary**

This review provides an update on the current clinical and preclinical understanding of chemotherapy induced peripheral neuropathy (CIPN). The overview of the clinical syndrome, includes a review of its assessment, diagnosis and treatment. CIPN is caused by several widely-used chemotherapeutics including paclitaxel, oxaliplatin, bortezomib. Severe CIPN may require dose reduction, or cessation, of chemotherapy, impacting on patient survival. While CIPN often resolves after chemotherapy, around 30% of patients will have persistent problems, impacting on function and quality of life. Early assessment and diagnosis is important, and we discuss tools developed for this purpose. There are no effective strategies to prevent CIPN, with limited evidence of effective drugs for treating established CIPN. Duloxetine has moderate evidence, with extrapolation from other neuropathic pain states generally being used to direct treatment options for CIPN. The preclinical perspective includes a discussion on the development of clinically-relevant rodent models of CIPN and some of the potentially modifiable mechanisms that have been identified using these models. We focus on the role of mitochondrial dysfunction, oxidative stress, immune cells and changes in ion channels from summary of the latest literature in these areas. Many causal mechanisms of CIPN occur simultaneously and/or can reinforce each other. Thus, combination therapies may well be required for most effective management. More effective treatment of CIPN will require closer links between oncology and pain management clinical teams to ensure CIPN patients are effectively monitored. Furthermore, continued close collaboration between clinical and preclinical research will facilitate the development of novel treatments for CIPN.

## **Introduction**

Neuropathic pain, defined as "*Pain caused by a lesion or disease of the somatosensory nervous system*" is a challenging clinical problem, with up to 8% of the population suffering from moderate to severe pain.<sup>1,2,3</sup> Neuropathic pain may have an even greater impact on patients than other chronic pain syndromes with affected individuals rating their quality of life as "worse than death", on the EQ-5D, a validated quality of life measure<sup>3</sup>. Unfortunately, many modern chemotherapeutic agents can cause both acute and chronic peripheral neuropathy - chemotherapy induced peripheral neuropathy (CIPN)<sup>4</sup>. During oncological treatment, the severity of the acute syndrome may require reducing the dose of chemotherapy or even stopping it, with potential impact on tumour control and survival.

Chemotherapy-induced painful neuropathy (CIPN) is a major dose-limiting side effect of several first-line chemotherapeutic agents<sup>5-10</sup>. CIPN is a challenging and complex pain syndrome that we have no effective preventive and limited treatment options for currently. CIPN can have a major and prolonged impact on quality of life for patients. As oncological treatments have advanced, cancer survival has increased significantly, with many patients either being cured of cancer or living for many years with cancer. Given the prevalence of the common cancers (e.g. breast, ovarian, colorectal) these chemotherapeutics counteract, CIPN affects several million patients worldwide each year. CIPN also places a significant economic burden on patients due to workloss and the healthcare system due to its prevalence<sup>11</sup>. Effective collaboration between preclinical and clinical researchers is needed to translate improved understanding of the underlying mechanisms into development of effective preventive and treatment strategies<sup>12</sup>. This review aims to provide an overview of the clinical syndrome, its assessment, diagnosis and treatment, and how our improved understanding of underlying mechanisms contribute to this. While there are, multiple factors contributing to CIPN, we will focus on the role of mitochondrial dysfunction, oxidative stress, immune cells and changes in ion channels in CIPN rodent models.

## **CIPN: The Clinical Syndrome**

CIPN usually presents as a typical "glove and stocking" neuropathy. Patients describe a range of predominantly sensory symptoms including numbness, parathesia, ongoing/spontaneous pain, hypersensitivity to mechanical and/or cold stimuli in their hands and feet. In more severe cases, loss of vibration sense and joint position sense contribute to the impact on function. Autonomic and motor dysfunction may also occur. Patients can have significant difficulty in essential daily functions including difficulty in fine finger movement such as buttoning clothing, and unsteady gait (numbness, loss of joint position sense); pain on walking (mechanical hypersensitivity); inability to remove items from a fridge, or exacerbation in cold weather (cold hypersensitivity). CIPN may present acutely, during chemotherapy, such as is commonly seen with platinum based compounds <sup>13</sup>. It may also occur after treatment has finished - a phenomenon known as "coasting" -where either mild neuropathy worsens, or new CIPN develops. This is challenging for oncologists, as there is no indication during chemotherapy to allow dose modification in order to reduce CIPN <sup>14</sup>. Pain and sensory abnormalities can persist for months or years following the cessation of chemotherapy <sup>5, 15, 16</sup>. Therefore, patients may well be cancer-free, but suffering a debilitating neuropathy evoked by their cancer treatment.

Peripheral neuropathy has been long associated with established drugs such as platinum agents (e.g. oxaliplatin), vinca alkaloids (e.g. vincristine), and taxanes (e.g. paclitaxel). However, newer, more targeted drugs, such as bortezomib, eribulin and ixabepilone <sup>4, 17</sup> are also associated with significant incidence of peripheral neuropathy. All of these chemotherapeutics have different mechanisms by which they evoke their anti-mitotic effects e.g. perturbation of microtubule dynamics, DNA cross-linking, proteasome inhibition. Whether all these drugs evoke neurotoxicity by similar mechanisms remains to be determined.

## **Prevalence and risk factors for CIPN**

The prevalence of CIPN varies between different agents, with reported rates varying from 19% to more than 85% <sup>18</sup>. While the agent and dose used is an important determining factor, there is no doubt that the lack of a gold standard agreed assessment tool impacts on reported rates of CIPN <sup>19</sup>.

A systemic review and meta-analysis of CIPN incidence and prevalence with paclitaxel, bortezomib, cisplatin, oxaliplatin, vincristine or thalidomide (solo or combination) treatment demonstrated the persistence of this disorder <sup>20</sup>. CIPN was observed in 68.1%, 60%, and 30% of patients, within the first month, at 3 months, and at  $\geq 6$  months, respectively, after cessation of chemotherapy, when looking at chemotherapy as a whole. While type of chemotherapy is important, at least part of the variability in reported prevalence was due to differences in the timing of assessment <sup>20</sup>.

A number of possible risk factors have been identified, including genetic factors, although there is a need for more systematic evaluation of potential contributory factors. A number of single nucleotide polymorphisms potentially associated with CIPN have been identified through Genome Wide Association Studies. Proteins with a range of functions have been identified, including axon outgrowth, sodium channels and neuronal apoptosis <sup>21-25</sup>. Studies of clinical risk factors are limited, often with small sample sizes. From the available data for CIPN, a history of neuropathy prior to starting chemotherapy (eg diabetic), impaired renal function with reduced creatinine clearance, and a history of smoking may all increase risk of developing CIPN. The cumulative dose of chemotherapy is well recognised as a major risk factor, with growing interest in the effect of levels of circulating growth factors or other biological markers as a means of early identification of quantifiable risk factors <sup>20</sup>.

### **Assessment and diagnosis of CIPN**

There is currently no widely accepted, standardized assessment approach for diagnosis of CIPN per se. There are a number of guidelines on assessment and diagnosis of neuropathic pain in general, which may be useful in CIPN <sup>26-28</sup>. Onset of symptoms during, or shortly after, chemotherapy is normally described, often affecting feet first, then with impairment of sensation in fingers and hands. If patients describe abnormalities in sensation, or these are detected on clinical examination, then CIPN should be suspected. Early identification allows treatment decisions about continuation, or not, of chemotherapy to be better informed, as well as allowing initiation of anti-neuropathic agents, if appropriate <sup>29, 30</sup>.

Accurate understanding of the epidemiology of CIPN, early identification and treatment of the clinical problem and evaluation of new treatments would all be improved by a standardized approach. The aim of the CI-PeriNomS Study Group was to assess reproducibility and validity of existing measures, and if necessary develop a simple and reproducible assessment for CIPN to try and meet this need <sup>31</sup>. A number of the tools available for assessing CIPN have been robustly assessed and show good reliability and validity (see table 1) <sup>32</sup>. From this, abnormalities in monofilament testing and vibration perception may be useful in identifying CIPN <sup>33-35</sup>. Quantitative sensory testing (QST) is recommended as part of neuropathic pain assessment, and may have clinical utility in early assessment of CIPN. <sup>26, 27</sup>. There is some evidence that there are baseline QST deficits in cancer patients even prior to starting chemotherapy, that may predispose them to developing CIPN, raising the possibility that the cancer process itself may be involved <sup>36</sup>. Sensory abnormalities, for example with raised detection threshold of small bumps of variable quantified sizes ("bumps test"), with an associated reduction in Meissner's Corpuscles counts were found in patients before chemotherapy. Furthermore, long-term outcome for pain and sensory disturbances during chemotherapy was more pronounced in patients with baseline sensory deficits compared to patients who presented without deficits <sup>37, 38</sup>.

In patients with established CIPN QST abnormalities indicate deficits in A-beta fibre (altered touch detection to monofilaments, and altered bumps test), A-delta fibre (impaired sharpness detection) and C-fibre (pin prick) function. The importance of these findings is that classes of primary afferent fibers show differential impairments, indicating that the underlying mechanisms are particular to nerve fiber types as opposed to a non-specific toxicity <sup>16, 39, 40</sup>. Changes in QST have been shown to be associated with alterations in epidermal nerve fibre density, occurring in a pattern that matches the distribution of symptoms, such that the lowest counts are in the painful area, but get progressively higher moving proximal where the symptoms change to numbness and then to no complaint. The decrease in ENF density matches the QST data in these patients in that they had elevated pain and sharpness detection thresholds in the fingers and palm <sup>16, 41</sup>. Currently, routine clinical assessment of patients undergoing chemotherapy often does not include measurement of

sensory function. Based on the current evidence, simple tests of vibration sense or light touch may be useful clinical tools, that merit further study.

### **Prevention and treatment of CIPN**

Many RCTs have investigated potential therapies for the prevention of CIPN development or reversal of established CIPN. However, clinical practice guidelines from the American Society of Clinical Oncology (ASCO) following a systematic review of this literature did not recommend any agent for the prevention of CIPN. There have been a number of small trials of agents to prevent CIPN developing, ranging from acetyl-L-carnitine to vitamin E, with no evidence of major benefit <sup>30</sup>.

Treatment of CIPN is mainly based on evidence from other chronic neuropathic pain conditions, rather than specifically targeting underlying mechanisms in CIPN. A comprehensive review of the evidence base for all types of neuropathic pain found some overestimation of the treatment effect (~10%), with combined numbers needed to treat (NNTs) being modest (table 2). In the ASCO guidelines, specifically about CIPN, a moderate recommendation was made for duloxetine in the treatment of established CIPN. Generally, whilst evidence for agents used in other neuropathic pain syndromes (as shown in table 2) is lacking for CIPN, it is still reasonable to try them, after appropriate discussion with the patient. There was also a weak recommendation for a topical gel containing baclofen (10mg), amitriptyline (40mg) and ketamine (20mg), based on one study <sup>30, 42</sup>.

As preventative/curative treatment options for CIPN are currently limited, dose reduction or cessation of chemotherapy is often associated with the emergence of symptoms of neuropathy <sup>43</sup>. Thus, CIPN potentially impacts on both the quality of life and survival of cancer patients. There are a number of areas of therapeutic interest arising from preclinical studies.

### **Animal models of CIPN**

Developing rodent models of CIPN which replicate all the symptoms that patients report is somewhat challenging because numbness, tingling and ongoing pain all rely on verbal report from the patient. Thus, most studies have focussed on measuring evoked pain-like behaviours as has been the case for preclinical studies with other chronic pain models. Investigations into novel measures of



spontaneous pain in CIPN rats are ongoing and paclitaxel-induced deficits in burrowing behaviour and voluntary wheel running were recently observed (data shown at NeupSIG 2017). Rat and mice models of CIPN have been reported following administration of different chemotherapeutics including paclitaxel, docetaxel, vincristine, cisplatin, oxaliplatin, bortezomib <sup>44, 45</sup>. Initial work investigating the neurotoxicity associated with paclitaxel involved direct application of paclitaxel to peripheral nerves resulting in degeneration and specific aggregation of microtubules <sup>46-48</sup>. However, the relevance of such local application of chemotherapy to understanding mechanisms of CIPN that are evoked by systemic administration is limited due to the high endoneurial concentration. In later studies, rodent models of paclitaxel-induced painful neuropathy were developed using systemic paclitaxel administered via intravenous or intraperitoneal routes e.g. <sup>49, 50</sup>. In fact, most of the dosing regimens (reviewed in <sup>44, 45</sup>) utilized to create rodent CIPN models involve intermittent systemic administration to mimic cycles of chemotherapy as opposed to daily dosing.

Typically, most models of CIPN involve the solo administration of a given chemotherapeutic in the absence of tumour load. However, there are reports using a rat model possessing an implanted subcutaneous tumour with combined paclitaxel and cisplatin treatment <sup>51, 52</sup>. Animal health must be considered when employing rodent models of CIPN for ethical reasons and practical feasibility. Pain-like behaviours cannot be accurately assessed if rodents are ill due to systemic toxicity and thus lethargic/unresponsive to hind paw stimulation. Although rodent models of CIPN with a tumour could be considered as more clinically relevant, the practical/ethical issues of this should not be underestimated. In addition, as chemotherapy is often received after surgical removal of the tumour to eliminate possible micro-metastases, modelling CIPN through chemotherapy administration alone is a valid approach. For new preclinical investigations, the use of established intermittent dosing schedules to generate CIPN models is encouraged as much as possible. Wide adoption of the same dosing schedules across different laboratories would further understanding of causal mechanisms of CIPN and enhance reproducibility.

CIPN models typically display sensory symptoms such as mechanical allodynia, mechanical hyperalgesia, cold allodynia, and in some reports, heat hyperalgesia. Oxaliplatin-induced peripheral neuropathy is associated with an acute cold/mechanical hypersensitivity within hours of administration and a chronic neuropathy. Both syndromes can be replicated in rats and mice at a range of systemic doses <sup>45</sup>. Studies with paclitaxel demonstrated that the cumulative dose administered affects both the integrity of peripheral nerves and the behavioural symptoms evoked. Systemic administration of low-doses of paclitaxel (<10mg/kg cumulative dose) did not markedly affect neural microtubule structure or cause aggregation <sup>53</sup> as observed following epineural administration <sup>46-48</sup>. Following low dose paclitaxel, neurodegeneration was not evident mid-axon or in the DRG <sup>53</sup>, however there is a loss of intraepidermal nerve fibres (IENFs) <sup>54, 55</sup>. Greater degrees of degeneration in peripheral nerves and the DRG were caused by larger cumulative doses of paclitaxel (<16mg/kg) in a dose-dependent manner <sup>49, 56-58</sup>. The dose-dependent effects of paclitaxel administration have also been observed in patients, where the incidence and severity of neuropathic signs and symptoms increased relative to increasing cumulative doses of paclitaxel <sup>59</sup>. Paclitaxel-evoked behaviours in rodents are also dose-dependent. Mechanical and cold allodynia without motor deficit are observed at low doses <sup>50, 60, 61</sup>. In contrast, heat hypoalgesia and motor deficit is reported at high doses, which is likely indicative of significant neurodegeneration <sup>49, 62-64</sup>. Collectively, these studies indicate that pain associated with CIPN is not necessarily a result of marked peripheral nerve degeneration.

### **Role of mitochondrial dysfunction in CIPN**

Over the last decade, research has identified mitochondrial dysfunction has a significant contributory factor in CIPN. The first preclinical evidence identified swollen and vacuolated mitochondria in both myelinated axons and C-fibres in peripheral sensory nerves following systemic paclitaxel <sup>53</sup>. Paclitaxel-induced changes in neuronal mitochondria, correlated to the development and maintenance of paclitaxel-induced pain syndrome i.e. present prior to and during paclitaxel-induced pain, but absent when the pain syndrome had resolved <sup>53</sup>. These low dose paclitaxel-induced mitochondrial changes in C-fibres and myelinated axons have since been confirmed by many groups

<sup>65-70</sup>. Paclitaxel increased the incidence of swollen/vacuolated mitochondria in dorsal root C-fibres and A-fibres <sup>66</sup> and the DRG <sup>70-72</sup>, but not in the ventral root or Schwann cells <sup>66</sup>. There is also evidence for mitochondrial dysfunction from the clinical literature. Two case reports show electron micrographs of sensory axons containing swollen, vacuolated mitochondria in sural nerve biopsies from patients with chemotherapy-induced neuropathy evoked by paclitaxel <sup>73</sup> and docetaxel <sup>74</sup>. Swollen/vacuolated mitochondria have also been observed in C-fibres and A-fibres of rat models of oxaliplatin-induced painful neuropathy <sup>75</sup> and bortezomib-induced painful neuropathy <sup>76</sup>. The presence of swollen mitochondria does not indicate the nature of mitochondrial dysfunction evoked. This can be determined through assays of mitochondrial function. Significant decreases in complex I-stimulated and complex II-stimulated respiration in sciatic nerves from paclitaxel-, oxaliplatin and bortezomib-treated rats were observed prior to, and during chemotherapy-induced pain behaviour <sup>76, 77</sup>. Recent data discussed at NeupSIG 2017 demonstrates the maximal respiration and spare reserve capacity (the respiratory ability of the cell to overcome stress) were significantly decreased in DRG neurons from paclitaxel-treated rats prior to pain onset <sup>78</sup>. During paclitaxel-induced pain, these OXPHOS-driven respiratory deficits in DRG neurons resolved, yet DRG neurons become more glycolytic in their function and preferentially switch to glycolysis from OXPHOS. The switch to glycolysis may be an adaptive mechanism to produce less ROS and prevent apoptosis through the increased pentose phosphate pathway activity and elevated glutathione peroxidase levels <sup>79</sup>. These paclitaxel-evoked changes in bioenergetics are also associated with decreased ATP. Prior to and during paclitaxel-induced pain, less ATP was present in DRG neurons *in situ* <sup>78</sup>, yet deficits in ATP production in peripheral nerves are only observed during maximally stimulated conditions <sup>77, 80</sup>. There was no change in the bioenergetic status of DRG neurons of paclitaxel-treated rats when the pain syndrome had resolved <sup>78</sup> further indicating the contribution of these factors to the development and maintenance of paclitaxel-induced pain.

Several studies have examined *in vivo* pharmacological modulation of the mitochondrial electron transport chain (ETC) in CIPN models <sup>81-83</sup>. Differential effects of specific complex inhibition have been observed (reviewed in <sup>84</sup>) which may be explained by route of drug administration, inhibitor in

question or time point examined post chemotherapy administration. For example, antimycin A (complex III inhibitor) significantly inhibited the development of paclitaxel-induced mechanical hypersensitivity when given before and during paclitaxel administration, but had no effect when given after paclitaxel administration <sup>83</sup>. Other pharmacological reagents that directly interact with mitochondria and their function in different ways have shown their potential to alleviate CIPN <sup>53, 69, 70, 85-87</sup>. Acetyl-L-carnitine (ALC) is involved in free fatty acid oxidation and acts as an antioxidant. Prophylactic ALC administration prevented the development of paclitaxel-induced mechanical hypersensitivity <sup>53</sup>; paclitaxel-evoked increase in swollen/vacuolated mitochondria in C-fibres <sup>65</sup>; and paclitaxel-, oxaliplatin and bortezomib-evoked compromises in mitochondrial respiration in sciatic nerves <sup>76, 77</sup>. Despite promising preclinical data <sup>88-91</sup> and an open-label phase II trial of CIPN patients <sup>92</sup>, a placebo-controlled RCT reported prolonged ALC treatment was associated with more severe paclitaxel-evoked neurotoxicity in breast cancer patients <sup>93</sup>. TRO19622 /Olesoxime, which directly binds to mitochondria (at the mPTP), attenuated chemotherapy-induced mechanical hypersensitivity and IENF loss, but had no effect on paclitaxel-induced spontaneous discharge in C- and A-fibres <sup>85, 86</sup>. Inhibition of mitochondrial fission significantly attenuated oxaliplatin-induced mechanical hyperalgesia <sup>87</sup>. Pifithrin- $\mu$ , an inhibitor of mitochondrial p53 accumulation, prevented development of paclitaxel- and cisplatin-induced mechanical hypersensitivity<sup>70</sup>. Pifithrin- $\mu$  also prevented paclitaxel-evoked mitochondrial changes in sensory neurons and IENF loss with evidence of enhancement of paclitaxel's anti-tumour effects <sup>70</sup>. Similarly, minoxidil was recently shown to prevent paclitaxel-evoked nociceptive behaviour and mitochondrial changes in sensory neurons accompanied with augmentation of paclitaxel's anti-tumour action <sup>69</sup>.

### **Role of oxidative stress in CIPN**

Mitochondria are a major source of reactive oxygen species (ROS) and increased ROS production can be a consequence of mitochondrial dysfunction. However, there are other cellular sources of ROS and reactive nitrogen species (RNS). Evidence for ROS involvement in neuropathic pain dates back to the 1990s e.g. <sup>94</sup> and ROS/RNS have multiple effects on neuronal excitability (reviewed in <sup>95</sup>). The role of oxidative stress in CIPN has been examined *in vivo* using pharmacological reagents that scavenge ROS. PBN, a non-specific ROS scavenger, inhibited the

development of paclitaxel-induced mechanical hypersensitivity<sup>96, 97</sup>; reversed established paclitaxel-induced mechanical & cold hypersensitivities<sup>96, 97</sup>; and bortezomib-induced mechanical hypersensitivity<sup>98</sup>. High doses of TEMPOL, a superoxide dismutase mimetic, inhibited the development and maintenance of paclitaxel-induced mechanical hypersensitivity<sup>97, 99</sup>, but was ineffective on cold allodynia<sup>97</sup>. Another SOD mimetic, MnL4, inhibited oxaliplatin-induced mechanical and cold hypersensitivities<sup>100</sup>. Peroxynitrite decomposition catalysts have been shown to reverse established paclitaxel-induced mechanical hypersensitivity<sup>101</sup> and to also prevent the development of mechanical hypersensitivity induced by paclitaxel, oxaliplatin and bortezomib<sup>80, 101</sup>. Novel mitochondria-targeted antioxidants have also been evaluated. SS-31 attenuated oxaliplatin-induced cold & mechanical hypersensitivities<sup>102</sup>. MitoVitE attenuated the development of paclitaxel-induced mechanical hypersensitivity<sup>103</sup>.

Other studies have measured ROS/RNS levels within the nociceptive system of CIPN models *in vivo* to understand the cellular basis/location of oxidative stress during CIPN. Increased RNS production was indicated in the spinal cord of paclitaxel-treated rats<sup>101</sup>. In addition, increased ROS and RNS levels were seen in lumbar DRG following chronic oxaliplatin treatment in mice<sup>102</sup>. Data discussed at NeupSIG 2017 showed how oxidative stress is linked to the development, maintenance and resolution of CIPN. ROS levels were elevated in superficial spinal neurons and non-peptidergic (IB4+) DRG neurons, *in vivo*, prior to the onset of paclitaxel-induced pain behaviour<sup>79</sup>, suggesting ROS is an initiating factor. The preferential elevation of ROS in IB4+ neurons could suggest a direct mechanism by which TRPA1 channels, known neuronal ROS sensors and predominantly expressed on IB4+ DRG neurons<sup>104</sup>, contribute to paclitaxel-induced pain<sup>105, 106</sup>. To understand how ROS was managed endogenously, we also examined the activity of different antioxidant enzymes in the DRG and peripheral sensory nerves during the timecourse of paclitaxel-induced painful neuropathy. Enhanced activity of mitochondrial and cellular endogenous antioxidant enzymes in the DRG and peripheral nerves was observed, however this was inadequate and delayed in its onset leading to excessive ROS in peripheral sensory axons<sup>79</sup>. Others have demonstrated an impaired mitochondrial antioxidant response following paclitaxel,

oxaliplatin and bortezomib<sup>80</sup>. Collectively these *in vivo* preclinical studies suggest that mitochondrial ROS is causal to the development and maintenance of CIPN.

### **Role of immune cells in CIPN**

In addition to effects on mitochondria and the generation of oxidative stress, chemotherapy agents also engage the innate immune system to induce peripheral neuropathy. A key mediator in this is the toll-like receptors (TLR). These are transmembrane proteins that normally function to detect various pathogens, TLR4 specialized to detect bacterial pathogens and TLR3 specialized to detect viral pathogens by example. TLR4 is also activated by several chemotherapeutics<sup>107</sup>. TLR4 and its immediate downstream signals are increased in the DRG of rats with paclitaxel-induced hyperalgesia; and this hyperalgesia can be prevented by co-treating animals with TLR4 antagonists during chemotherapy<sup>108, 109</sup>. Similarly, mice with a genetic knockout of either TLR4 or TLR3 fail to develop hyperalgesia following treatment with cisplatin<sup>110</sup>. It appears that a key result of TLR4 activation by chemotherapeutics is to increase pro-inflammatory cytokine expression in the peripheral and central nervous systems. The C-C motif chemokine ligand 2 (CCL2, also called monocyte chemoattractant protein 1 or MCP1) and its receptor CCR2 are increased small DRG neurons that appear to be nociceptors and in spinal astrocytes in rats with paclitaxel related CIPN.<sup>111</sup>. Gene knockdown or knockout of CCR2 or use of a chemical CCR2 antagonist reduced neuropathic pain in mice<sup>112 113</sup>.

Macrophages are normally not found in large numbers in the DRG, yet the immediate result of the paclitaxel-induced increase in CCL2 in the DRG is a marked increase in these cells within the DRG within a few days of treatment<sup>114</sup>. These macrophages have a pro-inflammatory phenotype that results in increased levels of Interleukin-1 (IL-1) and Tumor necrosis factor alpha (TNF $\alpha$ ) in the DRG. A number of studies have shown that pro-inflammatory cytokines such as these produce hyperalgesia to both thermal and mechanical stimuli<sup>115, 116</sup>. This occurs by a number of mechanisms. IL-1 and TNF $\alpha$  act on both spinal and DRG neurons to lower their threshold of activation, a process

termed sensitization, and to induce spontaneous discharges<sup>117, 118, 119</sup>. TNF $\alpha$  specifically also suppresses the signalling of spinal GABA neurons leading to central disinhibition of pain signalling<sup>120</sup>. IL-1 and TNF $\alpha$ , as well as IL-6 also increase the release of bradykinin, serotonin, and histamine that further augments pro-inflammatory processes<sup>121, 122</sup>. Increased production and release of IL-1, TNF $\alpha$  and CCL2 is a shared effect following administration of several chemotherapeutics including paclitaxel<sup>123</sup>, cisplatin<sup>124</sup> and vincristine<sup>125</sup>. Importantly given that both neurons and glial cells express receptors for these cytokines and can also produce these following activation this mechanism has the potential to become self-sustaining<sup>126</sup>.

Increased levels of IL-1, TNF $\alpha$  and CCL2 in the DRG and spinal cord produce alterations in Schwann cells along peripheral axons, satellite cells in the DRG, and astrocytes in the spinal cord that further contribute to chemotherapy related hyperalgesia. A constant observed following treatment with several different chemotherapy agents is that astrocytes show a down-regulation in the expression of glutamate transporters. These are key to clearing synaptically released glutamate and dysfunction in this process leads to hyperexcitability of spinal neurons. As referenced above, the activation of Schwann cells leads to further release cytokines IL-1 and TNF $\alpha$ <sup>127 128, 129</sup> (see more below), but also leads to the extirpation of these cells from peripheral axons<sup>56</sup>, resulting in reduced action potential propagation as well as longer term reduced protection and nourishment of nerve fibers. Satellite cells in the DRG react similarly to Schwann cells when exposed to chemotherapy agents<sup>130</sup> resulting in pro-apoptotic stress in DRG neurons. Satellite cells also increase their expression of gap junctions following chemotherapy treatment. Although the exact basis is unclear this appears to further promote pain signalling given that gap junction blockers produce an analgesic effect in CIPN mice<sup>131</sup>. An unusual aspect of glial response in the spinal cord is that astrocytes, but not microglia become activated in CIPN<sup>132, 133, 134</sup>. In many other types of neuropathic pain a primary role is assigned to microglia that does not appear to be involved in CIPN. Like in Schwann cells, inhibitors of gap junctions in astrocytes results in reduced hyperalgesia in CIPN, and a similar anti-hyperalgesic response is produced using the glial inhibitor minocycline<sup>135, 136</sup>.

## **Changes in ion channels in CIPN**

The net result of the activation of innate immune responses in the DRG and spinal cord is the induction of hyperexcitability and ectopic spontaneous activity in both peripheral and spinal neurons. These, in turn are due to alterations in neuronal ionic homeostasis as revealed by ion channel microarray <sup>137</sup>. By example, given the primacy of Na<sup>+</sup> ions in generating electrical activity in neurons, it is almost expected that alterations in voltage-gated sodium channels occur in CIPN. Recent work by our group that will be presented at NeuPSIG 2017 shows that the expression and function of the voltage-gated sodium channel Nav1.7 is markedly increased in DRG neurons following paclitaxel treatment and contributes directly to the development of ectopic spontaneous activity in nociceptors (Li et al, 2017, submitted). As well, prolonged opening in voltage-gated Na<sup>+</sup> channels is produced by oxalate, a metabolite of oxaliplatin that results in lowered activation threshold and ectopic firing in DRG neurons <sup>138, 139</sup>. Enhanced activity in sodium channels would appear to reflect the increased peripheral axonal excitability seen prior to symptom expression in patients <sup>140, 141</sup>. Beyond the spinal cord and DRG, increased expression of voltage gated sodium channels is also found in forebrain regions following paclitaxel treatment <sup>142</sup>. A caveat to this latter observation is that forebrain changes in sodium channels would be secondary to alterations occurring elsewhere given the poor penetrance of paclitaxel to the CNS. These preclinical observations are supported by clinical findings in that voltage-gated sodium channel blockers, such carbamazepine, that have found success in treating some <sup>143</sup>, but not all neuropathic pain patients <sup>144</sup>.

A second ion channel that is key in resulting neuronal excitability is that for potassium. Alterations in K<sup>+</sup> channel function have been noted at several levels of the neuraxis in CIPN. By example, K<sup>+</sup> channels are down-regulated in the cortex and in primary afferent neurons of rats with oxaliplatin CIPN <sup>145, 146</sup>; and in the DRG of rats with paclitaxel-related CIPN <sup>137</sup>. In congruity with the observed changes in Na<sup>+</sup> and K<sup>+</sup> channels just noted others have reported an increased expression in hyperpolarization-activated channels (HCNs) that are permeable to both ions in CIPN <sup>147</sup>. Mathematical modelling of the consequences of the observed changes in Na<sup>+</sup> and K<sup>+</sup> channels indicates that these account well for the observed hyper-excitability in nociceptors that occurs in



oxaliplatin CIPN<sup>148</sup>. The therapeutic potential of targeting K<sup>+</sup> channels in CIPN is supported by the observation that the K<sup>+</sup> channel opener, retigabine, reduced signs of hyperalgesia in mice with cisplatin-related CIPN<sup>149</sup>.

Voltage-gated calcium channels are key in regulating synaptic transmission and so not surprisingly also implicated in the hyper-excitability in CIPN. DRG neurons show increased levels of voltage-gated calcium channel mRNA following paclitaxel treatment in mice<sup>150</sup>. Antagonists to voltage-gated calcium channels including gabapentin and ethosuximide were both effective in reducing signs of hyperalgesia in rodents with paclitaxel- and vincristine-induced CIPN<sup>60, 151</sup>. Consistent with these findings is that paclitaxel treatment was shown to alter calcium metabolism in primary afferent fibers<sup>152</sup> and treatment with minoxidil reversed this effect while also ameliorating the behavioural signs of paclitaxel-related CIPN<sup>69</sup>.

A large group of non-selective cation channels specifically localized in nociceptors that are involved in CIPN symptoms is the transient receptor potential (TRP) channels. Specifically, the TRP vanilloid 1 (TRPV1) and the TRP ankyrin 1 (TRPA1) subgroups have been implicated in CIPN-related pain. TRPV1, commonly also known as the receptor for capsaicin (the active ingredient in hot chili peppers) is physiologically activated by protons, heat above 42°C, and endogenous lipids produced during inflammation (for review, see<sup>153</sup>). The sensation produced by activation of TRPV1 are exactly those that are experienced by CIPN patients<sup>16, 41</sup>, in cutaneous nociceptors TRPV1 produces burning<sup>154</sup>, while in deep tissue nociceptors TRPV1 produces deep aching pain<sup>155, 156</sup>. Paclitaxel activates and sensitizes the function of TRPV1 and TRPV1 antagonists produce analgesia in paclitaxel-related CIPN<sup>157</sup>. Similarly treatment with either bortezomib or cisplatin produced an increase in TRPV1 expression in DRG and spinal cord in mice<sup>158, 159</sup>. Paclitaxel directly interacts with the TRPV1 channel to produce both an acute facilitation of signalling and also produces a long-term alteration of channel desensitization. The acute interaction has also been validated in human DRG neurons<sup>160</sup>. Parallel studies suggest that

oxaliplatin also sensitizes the TRPV1 and that this effect is mediated by the G-protein coupled receptor G2A <sup>161</sup>.

TRP ankyrin 1 (TRPA1) is often colocalized with TRPV1 and is activated by formalin, allyl isothiocyanate, and acrolein; and by temperatures below 17°C <sup>162</sup>. Given that activation of TRPA1 is activated by noxious cold stimuli in animals<sup>163</sup>, it has been suggested that this channel may mediate the acute hypersensitivity to cold observed in patients following oxaliplatin treatment. Preclinical studies using oxaliplatin appear to support this view<sup>164, 165</sup> and appear to also be generalizable to paclitaxel-induced cold hyperalgesia <sup>105</sup>. Preclinical studies have further detailed that chronic symptoms of CIPN may be mediated by chemotherapy-induced activation of proteinase-activated receptors (PARs) that activate phospholipase C, protein kinase A and protein kinase C epsilon that then sensitize TRPA1 as well as TRPV1 and TRPV4 channels, respectively <sup>106</sup>. Further support for a role of TRPA1 in CIPN is that receptor deficient mice were shown to be resistant to both oxaliplatin- and bortezomib-related CIPN<sup>167</sup>. Interestingly, in the context of previous discussion on oxidative stress, TRPA1 mediates neuropathic pain in trigeminal neurons downstream to the activation of macrophages/monocytes and their generation of oxidative stress <sup>168</sup>. Yet, human psychophysical studies suggest that even though noxious cold activates TRPA1 in rodents this may not be true in humans<sup>166</sup>, indicating that perhaps one final TRP channel may have an important role.

The transient receptor potential melastatin 8 (TRPM8) channel is activated by mild cool stimuli between 25 and 28°C and chemically by menthol <sup>169</sup> and has been implicated as analgesic when activated in some nerve injury models <sup>170</sup>. Some have suggested that TRPM8 could mediate cold-hyperalgesia in humans in CIPN. Yet, others have shown that topical menthol produces analgesia in paclitaxel CIPN patients <sup>171</sup> and this has been supported in a recent proof-of-concept study <sup>172</sup>. Other receptors subtypes including A3 adenosine receptors <sup>173</sup>, 5HT2A receptors <sup>174, 175</sup>, sigma-1 receptors<sup>68</sup> and mGluR5 receptors <sup>176</sup> have been implicated in CIPN and could prove potential avenues for new treatments.

## Conclusions

Preclinical models of CIPN can provide vital insight into the neurotoxic mechanisms that initiate and maintain CIPN. Compared to other chronic pain conditions, differential analgesic effects are observed in both CIPN patients and rodent models suggesting different causal mechanisms for CIPN. Many of the causal mechanisms of CIPN described in this review occur simultaneously and/or can reinforce each other. It seems likely therefore, that effective future developments may use combination therapies to either prevent development of CIPN where possible, or direct effective treatment for CIPN. There are very few clinical trials of combination therapies in any type of neuropathic pain, and it may be that to detect a clinically significant effect, we need to reconsider how clinical trials for neuropathic pain are designed<sup>177-179</sup>. An additional complexity in trials of CIPN is the effect of cancer on the pathophysiology of the pain systems: we do need to address how to translate preclinical models of single morbidities (such as CIPN) to the often complex co-morbidities that are seen in our aging population. More effective treatment of CIPN will require closer links between oncology and pain management clinical teams to ensure CIPN patients are effectively monitored. Furthermore, continued close collaboration between clinical and preclinical research will facilitate the development of novel treatments for CIPN.

## Figure Legends

Figure 1: Summary of the pathophysiological events contributing to chemotherapy-induced peripheral neuropathy (CIPN) as highlighted in this review. The most common agents provoking CIPN are shown in the bubble in A and the sites of action for these compounds are indicated by the arrows. The structures are also labeled in A while in B the changes occurring in these structures with CIPN are summarized. Reproduced with permission from Boyette-Davis JA, Walters ET, Dougherty PM, Mechanisms involved in the development of chemotherapy induced peripheral neuropathy. *Pain Manag.* 5 (4): 285-296, 2015.

## References

- 1 van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *BJA* 2013; **111**: 13-8
- 2 Taxonomy ITFo. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. [http://www.wiasp-pain.org/AM/Template.cfm?Section=Classification\\_of\\_Chronic\\_Pain&Template=/CM/HTMLDisplay.cfm&ContentID=2687](http://www.wiasp-pain.org/AM/Template.cfm?Section=Classification_of_Chronic_Pain&Template=/CM/HTMLDisplay.cfm&ContentID=2687) 2012: 214

- 3 Torrance N, Lawson K, Afolabi E, et al. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: does the choice between the EQ-5D and SF-6D matter? *Pain* 2014; **155**: 1996-2004 doi: 10.1016/j.pain.2014.07.001
- 4 Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. *Curr Opin Neurol* 2015; **28**: 500-7
- 5 Dougherty PM, Cata JP, Cordella JV, Burton A, Weng HR. Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. *Pain* 2004; **109**: 132-42
- 6 Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004; **96**: 1682-91
- 7 Argyriou AA, Koltzenburg M, Polychronopoulos P, Papapetropoulos S, Kalofonos HP. Peripheral nerve damage associated with administration of taxanes in patients with cancer. *Crit Rev Oncol Hematol* 2008; **66**: 218-28
- 8 Argyriou AA, Polychronopoulos P, Iconomou G, et al. Incidence and characteristics of peripheral neuropathy during oxaliplatin-based chemotherapy for metastatic colon cancer. *Acta Oncol* 2007; **46**: 1131-7
- 9 Attal N, Bouhassira D, Gautron M, et al. Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: a prospective quantified sensory assessment study. *Pain* 2009; **144**: 245-52
- 10 Reyes-Gibby CC, Morrow PK, Buzdar A, Shete S. Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated with paclitaxel. *J Pain* 2009; **10**: 1146-50
- 11 Pike CT, Birnbaum HG, Muehlenbein CE, Pohl GM, Natale RB. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. *Chemotherapy research and practice* 2012; **2012**: 913848
- 12 Sikandar S, Dickenson AH. II. No need for translation when the same language is spoken. *BJA* 2013; **111**: 3-6
- 13 Wilson RH, Lehky T, Thomas RR, Quinn MG, Floeter MK, Grem JL. Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol* 2002; **20**: 1767-74
- 14 Cavaletti G, Alberti P, Frigeni B, Piatti M, Susani E. Chemotherapy-induced neuropathy. *Current Treatment Options in Neurology* 2011; **13**: 180-90
- 15 van den Bent MJ, van Raaij-van den Aarssen VJ, Verweij J, Doorn PA, Sillevius Smitt PA. Progression of paclitaxel-induced neuropathy following discontinuation of treatment. *Muscle Nerve* 1997; **20**: 750-2
- 16 Boyette-Davis JA, Cata JP, Zhang H, et al. Follow-up psychophysical studies in bortezomib-related chemoneuropathy patients. *J Pain* 2011; **12**: 1017-24
- 17 Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. [Review]. *Neuro-Oncology* 2012; **14 Suppl 4**: iv45-iv54
- 18 Fallon MT. Neuropathic pain in cancer. [Review]. *BJA* 2013; **111**: 105-11
- 19 Alberti P, Rossi E, Cornblath DR, et al. Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: two sides of the same coin. *Annals of Oncology* 2014; **25**: 257-64
- 20 Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain* 2014; **155**: 2461-70
- 21 Chhibber A, Mefford J, Stahl EA, et al. Polygenic inheritance of paclitaxel-induced sensory peripheral neuropathy driven by axon outgrowth gene sets in CALGB 40101 (Alliance). *Pharmacogenomics Journal* 2014; **14**: 336-42
- 22 Wheeler HE, Gamazon ER, Wing C, et al. Integration of cell line and clinical trial genome-wide analyses supports a polygenic architecture of Paclitaxel-induced sensory peripheral neuropathy. *Clinical Cancer Research* 2013; **19**: 491-9
- 23 Corthals SL, Kuiper R, Johnson DC, et al. Genetic factors underlying the risk of bortezomib induced peripheral neuropathy in multiple myeloma patients. *Haematologica* 2011; **96**: 1728-32
- 24 Baldwin RM, Owzar K, Zembutsu H, et al. A genome-wide association study identifies novel loci for paclitaxel-induced sensory peripheral neuropathy in CALGB 40101. *Clinical Cancer Research* 2012; **18**: 5099-109
- 25 Broyl A, Corthals SL, Jongen JL, et al. Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial. *Lancet Oncology* 2010; **11**: 1057-65
- 26 Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. *European Journal of Neurology* 2010; **17**: 1010-8
- 27 Haanpaa M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; **152**: 14-27
- 28 Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain. Redefinition and a grading system for clinical and research purposes. *Neurology* 2008; **70**: 1630-5

- 29 Alberti P, Cavaletti G. Management of side effects in the personalized medicine era: chemotherapy-induced peripheral neuropathy. [Review]. *Methods in Molecular Biology* 2014; **1175**: 301-22
- 30 Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; **32**: 1941-67
- 31 The CIPSG. CI-PERINOMS: chemotherapy-induced peripheral neuropathy outcome measures study. *Journal Of The Peripheral Nervous System* 2009; **14**: 69-71
- 32 Cavaletti G, Cornblath DR, Merkies IS, et al. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Annals of Oncology* 2013; **24**: 454-62
- 33 Griffith KA, Merkies IS, Hill EE, Cornblath DR. Measures of chemotherapy-induced peripheral neuropathy: a systematic review of psychometric properties. [Review]. *Journal Of The Peripheral Nervous System* 2010; **15**: 314-25
- 34 Griffith KA, Dorsey SG, Renn CL, et al. Correspondence between neurophysiological and clinical measurements of chemotherapy-induced peripheral neuropathy: secondary analysis of data from the CI-PeriNomS study. *Journal Of The Peripheral Nervous System* 2014; **19**: 127-35
- 35 Griffith KA, Couture DJ, Zhu S, et al. Evaluation of chemotherapy-induced peripheral neuropathy using current perception threshold and clinical evaluations. *Supportive Care in Cancer* 2014; **22**: 1161-9
- 36 Boyette-Davis JA, Eng C, Wang XS, et al. Subclinical peripheral neuropathy is a common finding in colorectal cancer patients prior to chemotherapy. *Clin Cancer Res* 2012; **18**: 3180-7
- 37 de Carvalho Barbosa M, Kosturakis AK, Eng C, et al. A quantitative sensory analysis of peripheral neuropathy in colorectal cancer and its exacerbation by oxaliplatin chemotherapy. *Cancer Res* 2014; **74**: 5955-62
- 38 Vichaya EG, Wang XS, Boyette-Davis JA, et al. Subclinical pretreatment sensory deficits appear to predict the development of pain and numbness in patients with multiple myeloma undergoing chemotherapy. *Cancer Chemother Pharmacol* 2013; **71**: 1531-40
- 39 Cata JP, Weng HR, Burton AW, Villareal H, Giralt S, Dougherty PM. Quantitative sensory findings in patients with bortezomib-induced pain. *J Pain* 2007; **8**: 296-306
- 40 Dougherty PM, Cata JP, Burton AW, Vu K, Weng HR. Dysfunction in multiple primary afferent fiber subtypes revealed by quantitative sensory testing in patients with chronic vincristine-induced pain. *J Pain Symptom Manage* 2007; **33**: 166-79
- 41 Boyette-Davis JA, Cata JP, Driver LC, et al. Persistent chemoneuropathy in patients receiving the plant alkaloids paclitaxel and vincristine. *Cancer Chemother Pharmacol* 2013; **71**: 619-26
- 42 Smith E, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. *JAMA* 2013; **309**: 1359-67
- 43 Bhatnagar B, Gilmore S, Goloubeva O, et al. Chemotherapy dose reduction due to chemotherapy induced peripheral neuropathy in breast cancer patients receiving chemotherapy in the neoadjuvant or adjuvant settings: a single-center experience. *SpringerPlus* 2014; **3**: 366
- 44 Authier N, Balayssac D, Marchand F, et al. Animal models of chemotherapy-evoked painful peripheral neuropathies. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* 2009; **6**: 620-9
- 45 Hopkins HL, Duggett NA, Flatters SJ. Chemotherapy-induced painful neuropathy: pain-like behaviours in rodent models and their response to commonly used analgesics. *Current opinion in supportive and palliative care* 2016; **10**: 119-28
- 46 Roytta M, Horwitz SB, Raine CS. Taxol-induced neuropathy: short-term effects of local injection. *J Neurocytol* 1984; **13**: 685-701
- 47 Roytta M, Raine CS. Taxol-induced neuropathy: further ultrastructural studies of nerve fibre changes in situ. *J Neurocytol* 1985; **14**: 157-75
- 48 Roytta M, Raine CS. Taxol-induced neuropathy: chronic effects of local injection. *J Neurocytol* 1986; **15**: 483-96
- 49 Cavaletti G, Cavalletti E, Montaguti P, Oggioni N, De Negri O, Tredici G. Effect on the peripheral nervous system of the short-term intravenous administration of paclitaxel in the rat. *Neurotoxicology* 1997; **18**: 137-45
- 50 Polomano RC, Mannes AJ, Clark US, Bennett GJ. A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug, paclitaxel. *Pain* 2001; **94**: 293-304
- 51 Boyle FM, Beatson C, Monk R, Grant SL, Kurek JB. The experimental neuroprotectant leukaemia inhibitory factor (LIF) does not compromise antitumour activity of paclitaxel, cisplatin and carboplatin. *Cancer Chemother Pharmacol* 2001; **48**: 429-34
- 52 Boyle FM, Wheeler HR, Shenfield GM. Amelioration of experimental cisplatin and paclitaxel neuropathy with glutamate. *J Neurooncol* 1999; **41**: 107-16
- 53 Flatters SJL, Bennett GJ. Studies of peripheral sensory nerves in paclitaxel-induced painful peripheral neuropathy: evidence for mitochondrial dysfunction. *Pain* 2006; **122**: 245-57

- 54 Siau C, Xiao W, Bennett GJ. Paclitaxel- and vincristine-evoked painful peripheral neuropathies: loss of epidermal innervation and activation of Langerhans cells. *Exp Neurol* 2006; **201**: 507-14
- 55 Boyette-Davis J, Xin W, Zhang H, Dougherty PM. Intraepidermal nerve fiber loss corresponds to the development of Taxol-induced hyperalgesia and can be prevented by treatment with minocycline. *Pain* 2011; **152**: 308-13
- 56 Cliffer KD, Siuciak JA, Carson SR, et al. Physiological characterization of Taxol-induced large-fiber sensory neuropathy in the rat. *Ann Neurol* 1998; **43**: 46-55
- 57 Cavaletti G, Bogliun G, Marzorati L, et al. Peripheral neurotoxicity of taxol in patients previously treated with cisplatin. *Cancer* 1995; **75**: 1141-50
- 58 Peters CM, Jimenez-Andrade JM, Jonas BM, et al. Intravenous paclitaxel administration in the rat induces a peripheral sensory neuropathy characterized by macrophage infiltration and injury to sensory neurons and their supporting cells. *Exp Neurol* 2007; **203**: 42-54
- 59 Postma TJ, Vermorken JB, Liefing AJ, Pinedo HM, Heimans JJ. Paclitaxel-induced neuropathy. *Ann Oncol* 1995; **6**: 489-94
- 60 Flatters SJL, Bennett GJ. Ethosuximide reverses paclitaxel- and vincristine-induced painful peripheral neuropathy. *Pain* 2004; **109**: 150-61
- 61 Smith SB, Crager SE, Mogil JS. Paclitaxel-induced neuropathic hypersensitivity in mice: responses in 10 inbred mouse strains. *Life Sci* 2004; **74**: 2593-604
- 62 Authier N, Coudore F, Eschaliere A, Fialip J. Pain related behaviour during vincristine-induced neuropathy in rats. *Neuroreport* 1999; **10**: 965-8
- 63 Apfel SC, Lipton RB, Arezzo JC, Kessler JA. Nerve growth factor prevents toxic neuropathy in mice. *Annals of Neurology* 1991; **29**: 87-90
- 64 Wang MS, Davis AA, Culver DG, Glass JD. Wild mice are resistant to paclitaxel (taxol) neuropathy. *Ann Neurol* 2002; **52**: 442-7
- 65 Jin HW, Flatters SJL, Xiao WH, Mulhern HL, Bennett GJ. Prevention of paclitaxel-evoked painful peripheral neuropathy by acetyl-L-carnitine: Effects on axonal mitochondria, sensory nerve fiber terminal arbors, and cutaneous Langerhans cells. *Exp Neurol* 2008; **210**: 229-37
- 66 Xiao WH, Zheng H, Zheng FY, Nuydens R, Meert TF, Bennett GJ. Mitochondrial abnormality in sensory, but not motor, axons in paclitaxel-evoked painful peripheral neuropathy in the rat. *Neuroscience* 2011; **199**: 461-9
- 67 Wu Y, Li J, Zhou J, Feng Y. Dynamic long-term microstructural and ultrastructural alterations in sensory nerves of rats of paclitaxel-induced neuropathic pain. *Chin Med J (Engl)* 2014; **127**: 2945-52
- 68 Nieto FR, Cendan CM, Canizares FJ, et al. Genetic inactivation and pharmacological blockade of sigma-1 receptors prevent paclitaxel-induced sensory-nerve mitochondrial abnormalities and neuropathic pain in mice. *Mol Pain* 2014; **10**: 11
- 69 Chen YF, Chen LH, Yeh YM, et al. Minoxidil is a potential neuroprotective drug for paclitaxel-induced peripheral neuropathy. *Sci Rep* 2017; **7**: 45366
- 70 Krukowski K, Nijboer CH, Huo X, Kavelaars A, Heijnen CJ. Prevention of chemotherapy-induced peripheral neuropathy by the small-molecule inhibitor pifithrin- $\mu$ . *Pain* 2015; **156**: 2184-92
- 71 Barriere DA, Rieusset J, Chanteranne D, et al. Paclitaxel therapy potentiates cold hyperalgesia in streptozotocin-induced diabetic rats through enhanced mitochondrial reactive oxygen species production and TRPA1 sensitization. *Pain* 2012; **153**: 553-61
- 72 Matsumura Y, Yokoyama Y, Hirakawa H, Shigeto T, Futagami M, Mizunuma H. The prophylactic effects of a traditional Japanese medicine, goshajinkigan, on paclitaxel-induced peripheral neuropathy and its mechanism of action. *Mol Pain* 2014; **10**: 61
- 73 Sahenk Z, Barohn R, New P, Mendell JR. Taxol neuropathy. Electrodiagnostic and sural nerve biopsy findings. *Arch Neurol* 1994; **51**: 726-9
- 74 Fazio R, Quattrini A, Bolognesi A, et al. Docetaxel neuropathy: a distal axonopathy. *Acta Neuropathol* 1999; **98**: 651-3
- 75 Xiao WH, Zheng H, Bennett GJ. Characterization of oxaliplatin-induced chronic painful peripheral neuropathy in the rat and comparison with the neuropathy induced by paclitaxel. *Neuroscience* 2012; **203**: 194-206
- 76 Zheng H, Xiao WH, Bennett GJ. Mitotoxicity and bortezomib-induced chronic painful peripheral neuropathy. *Exp Neurol* 2012; **238**: 225-34
- 77 Zheng H, Xiao WH, Bennett GJ. Functional deficits in peripheral nerve mitochondria in rats with paclitaxel- and oxaliplatin-evoked painful peripheral neuropathy. *Exp Neurol* 2011; **232**: 154-61
- 78 Duggett NA, Griffiths LA, Flatters SJL. Paclitaxel-induced painful neuropathy is associated with changes in mitochondrial bioenergetics, glycolysis and an energy deficit in dorsal root ganglia neurons. *Pain* 2017; **Apr 24 [epub]** doi: [10.1097/j.pain.0000000000000939](https://doi.org/10.1097/j.pain.0000000000000939)
- 79 Duggett NA, Griffiths LA, McKenna OE, et al. Oxidative stress in the development, maintenance and resolution of paclitaxel-induced painful neuropathy. *Neuroscience* 2016; **333**: 13-26

- 80 Janes K, Doyle T, Bryant L, et al. Bioenergetic deficits in peripheral nerve sensory axons during chemotherapy-induced neuropathic pain resulting from peroxynitrite-mediated post-translational nitration of mitochondrial superoxide dismutase. *Pain* 2013; **154**: 2432-40
- 81 Joseph EK, Levine JD. Mitochondrial electron transport in models of neuropathic and inflammatory pain. *Pain* 2006; **121**: 105-14
- 82 Xiao WH, Bennett GJ. Effects of mitochondrial poisons on the neuropathic pain produced by the chemotherapeutic agents, paclitaxel and oxaliplatin. *Pain* 2012; **153**: 704-9
- 83 Griffiths LA, Flatters SJL. Pharmacological modulation of the mitochondrial electron transport chain in paclitaxel-induced painful peripheral neuropathy. *J Pain* 2015; **16**: 981-94
- 84 Flatters SJL. The contribution of mitochondria to sensory processing and pain. *Progress in molecular biology and translational science* 2015; **131**: 119-46
- 85 Bordet T, Buisson B, Michaud M, et al. Specific antinociceptive activity of cholest-4-en-3-one, oxime (TRO19622) in experimental models of painful diabetic and chemotherapy-induced neuropathy. *J Pharmacol Exp Ther* 2008; **326**: 623-32
- 86 Xiao WH, Zheng FY, Bennett GJ, Bordet T, Pruss RM. Olesoxime (cholest-4-en-3-one, oxime): analgesic and neuroprotective effects in a rat model of painful peripheral neuropathy produced by the chemotherapeutic agent, paclitaxel. *Pain* 2009; **147**: 202-9
- 87 Ferrari LF, Chum A, Bogen O, Reichling DB, Levine JD. Role of Drp1, a key mitochondrial fission protein, in neuropathic pain. *J Neurosci* 2011; **31**: 11404-10
- 88 Pisano C, Pratesi G, Laccabue D, et al. Paclitaxel and Cisplatin-induced neurotoxicity: a protective role of acetyl-L-carnitine. *Clin Cancer Res* 2003; **9**: 5756-67
- 89 Ghirardi O, Lo Giudice P, Pisano C, et al. Acetyl-L-Carnitine prevents and reverts experimental chronic neurotoxicity induced by oxaliplatin, without altering its antitumor properties. *Anticancer Res* 2005; **25**: 2681-7
- 90 Ghirardi O, Vertechy M, Vesci L, et al. Chemotherapy-induced allodynia: neuroprotective effect of acetyl-L-carnitine. *In Vivo* 2005; **19**: 631-7
- 91 Flatters SJL, Xiao WH, Bennett GJ. Acetyl-L-carnitine prevents and reduces paclitaxel-induced painful peripheral neuropathy. *Neurosci Lett* 2006; **397**: 219-23
- 92 Bianchi G, Vitali G, Caraceni A, et al. Symptomatic and neurophysiological responses of paclitaxel- or cisplatin-induced neuropathy to oral acetyl-L-carnitine. *Eur J Cancer* 2005; **41**: 1746-50
- 93 Hershman DL, Unger JM, Crew KD, et al. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. *J Clin Oncol* 2013; **31**: 2627-33
- 94 Tal M. A novel antioxidant alleviates heat hyperalgesia in rats with an experimental painful peripheral neuropathy. *Neuroreport* 1996; **7**: 1382-4
- 95 Gamper N, Ooi L. Redox and nitric oxide-mediated regulation of sensory neuron ion channel function. *Antioxid Redox Signal* 2015; **22**: 486-504
- 96 Kim HK, Zhang YP, Gwak YS, Abdi S. Phenyl N-tert-butyl nitron, a free radical scavenger, reduces mechanical allodynia in chemotherapy-induced neuropathic pain in rats. *Anesthesiology* 2010; **112**: 432-9
- 97 Fidanboyu M, Griffiths LA, Flatters SJL. Global inhibition of reactive oxygen species (ROS) inhibits paclitaxel-induced painful peripheral neuropathy. *PLoS ONE* 2011; **6**: e25212
- 98 Duggett NA, Flatters SJL. Characterisation of a rat model of bortezomib-induced painful neuropathy. *Br J Pharmacol* 2017: Submitted
- 99 Kim HK, Hwang S-H, Abdi S. Tempol Ameliorates and Prevents Mechanical Hyperalgesia in a Rat Model of Chemotherapy-Induced Neuropathic Pain. *Frontiers in Pharmacology* 2017; **7**: 532
- 100 Di Cesare Mannelli L, Zanardelli M, Landini I, et al. Effect of the SOD mimetic MnL4 on in vitro and in vivo oxaliplatin toxicity: Possible aid in chemotherapy induced neuropathy. *Free Radic Biol Med* 2016; **93**: 67-76
- 101 Doyle T, Chen Z, Muscoli C, et al. Targeting the overproduction of peroxynitrite for the prevention and reversal of paclitaxel-induced neuropathic pain. *J Neurosci* 2012; **32**: 6149-60
- 102 Toyama S, Shimoyama N, Ishida Y, Koyasu T, Szeto HH, Shimoyama M. Characterization of acute and chronic neuropathies induced by oxaliplatin in mice and differential effects of a novel mitochondria-targeted antioxidant on the neuropathies. *Anesthesiology* 2014; **120**: 459-73
- 103 McCormick B, Lowes DA, Colvin L, Torsney C, Galley HF. MitoVitE, a mitochondria-targeted antioxidant, limits paclitaxel-induced oxidative stress and mitochondrial damage in vitro, and paclitaxel-induced mechanical hypersensitivity in a rat pain model. *Br J Anaesth* 2016; **117**: 659-66
- 104 Barabas ME, Kossyreva EA, Stucky CL. TRPA1 is functionally expressed primarily by IB4-binding, non-peptidergic mouse and rat sensory neurons. *PLoS One* 2012; **7**: e47988
- 105 Materazzi S, Fusi C, Benemei S, et al. TRPA1 and TRPV4 mediate paclitaxel-induced peripheral neuropathy in mice via a glutathione-sensitive mechanism. *Pflugers Arch* 2012; **463**: 561-9

- 106 Chen Y, Yang C, Wang ZJ. Proteinase-activated receptor 2 sensitizes transient receptor potential vanilloid 1, transient receptor potential vanilloid 4, and transient receptor potential ankyrin 1 in paclitaxel-induced neuropathic pain. *Neuroscience* 2011; **193**: 440-51
- 107 Byrd-Leifer CA, Block EF, Takeda K, Akira S, Ding A. The role of MyD88 and TLR4 in the LPS-mimetic activity of Taxol. *Eur J Immunol* 2001; **31**: 2448-57
- 108 Li Y, Zhang H, Zhang H, Kosturakis AK, Jawad AB, Dougherty PM. Toll-like receptor 4 signaling contributes to Paclitaxel-induced peripheral neuropathy. *J Pain* 2014; **15**: 712-25
- 109 Li Y, Zhang H, Kosturakis AK, et al. MAPK signaling downstream to TLR4 contributes to paclitaxel-induced peripheral neuropathy. *Brain Behav Immun* 2015; **49**: 255-66
- 110 Park HJ, Stokes JA, Corr M, Yaksh TL. Toll-like receptor signaling regulates cisplatin-induced mechanical allodynia in mice. *Cancer Chemother Pharmacol* 2014; **73**: 25-34
- 111 Zhang H, Boyette-Davis JA, Kosturakis AK, et al. Induction of monocyte chemoattractant protein-1 (MCP-1) and its receptor CCR2 in primary sensory neurons contributes to paclitaxel-induced peripheral neuropathy. *J Pain* 2013; **14**: 1031-44
- 112 Zhang ZJ, Dong YL, Lu Y, Cao S, Zhao ZQ, Gao YJ. Chemokine CCL2 and its receptor CCR2 in the medullary dorsal horn are involved in trigeminal neuropathic pain. *J Neuroinflammation* 2012; **9**: 136
- 113 Abbadie C, Lindia JA, Cumiskey AM, et al. Impaired neuropathic pain responses in mice lacking the chemokine receptor CCR2. *Proc Natl Acad Sci U S A* 2003; **100**: 7947-52
- 114 Zhang H, Li Y, de Carvalho-Barbosa M, et al. Dorsal Root Ganglion Infiltration by Macrophages Contributes to Paclitaxel Chemotherapy-Induced Peripheral Neuropathy. *J Pain* 2016; **17**: 775-86
- 115 Woolf CJ, Allchorne A, Safieh-Garabedian B, Poole S. Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumour necrosis factor alpha. *Br J Pharmacol* 1997; **121**: 417-24
- 116 Binshtok AM, Wang H, Zimmermann K, et al. Nociceptors Are Interleukin-1 beta Sensors. *Journal of Neuroscience* 2008; **28**: 14062-73
- 117 Sorkin LS, Xiao WH, Wagner R, Myers RR. Tumour necrosis factor-alpha induces ectopic activity in nociceptive primary afferent fibres. *Neuroscience* 1997; **81**: 255-62
- 118 Ozaktay AC, Cavanaugh JM, Asik I, DeLeo JA, Weinstein JN. Dorsal root sensitivity to interleukin-1 beta, interleukin-6 and tumor necrosis factor in rats. *European Spine Journal* 2002; **11**: 467-75
- 119 Onda A, Hamba M, Yabuki S, Kikuchi S. Exogenous tumor necrosis factor-alpha induces abnormal discharges in rat dorsal horn neurons. *Spine* 2002; **27**: 1618-24; discussion 24
- 120 Zhang H, Nei H, Dougherty PM. A p38 mitogen-activated protein kinase-dependent mechanism of disinhibition in spinal synaptic transmission induced by tumor necrosis factor-alpha. *J Neurosci* 2010; **30**: 12844-55
- 121 McMahon SB, Cafferty WB, Marchand F. Immune and glial cell factors as pain mediators and modulators. *Exp Neurol* 2005; **192**: 444-62
- 122 Vetere A, Choudhary A, Burns SM, Wagner BK. Targeting the pancreatic beta-cell to treat diabetes. *Nature reviews* 2014; **13**: 278-89
- 123 Zaks-Zilberman M, Zaks TZ, Vogel SN. Induction of proinflammatory and chemokine genes by lipopolysaccharide and paclitaxel (Taxol) in murine and human breast cancer cell lines. *Cytokine* 2001; **15**: 156-65
- 124 Basu S, Sodhi A. Increased release of interleukin-1 and tumour necrosis factor by interleukin-2-induced lymphokine-activated killer cells in the presence of cisplatin and FK-565. *Immunol Cell Biol* 1992; **70 ( Pt 1)**: 15-24
- 125 Weintraub M, Adde MA, Venzon DJ, et al. Severe atypical neuropathy associated with administration of hematopoietic colony-stimulating factors and vincristine. *J Clin Oncol* 1996; **14**: 935-40
- 126 Ledeboer A, Jekich BM, Sloane EM, et al. Intrathecal interleukin-10 gene therapy attenuates paclitaxel-induced mechanical allodynia and proinflammatory cytokine expression in dorsal root ganglia in rats. *Brain Behav Immun* 2007; **21**: 686-98
- 127 Cata JP, Weng HR, Lee BN, Reuben JM, Dougherty PM. Clinical and experimental findings in humans and animals with chemotherapy-induced peripheral neuropathy. *Minerva Anesthesiol* 2006; **72**: 151-69
- 128 Cavaletti G, Cavalletti E, Oggioni N, et al. Distribution of paclitaxel within the nervous system of the rat after repeated intravenous administration. *Neurotoxicology* 2000; **21**: 389-93
- 129 Ozturk G, Erdogan E, Anlar O, Kosem M, Taspinar M. Effect of leukemia inhibitory factor in experimental cisplatin neuropathy in mice. *Cytokine* 2005; **29**: 31-41
- 130 Takeda M, Takahashi M, Matsumoto S. Contribution of activated interleukin receptors in trigeminal ganglion neurons to hyperalgesia via satellite glial interleukin-1beta paracrine mechanism. *Brain Behav Immun* 2008; **22**: 1016-23
- 131 Warwick RA, Hanani M. The contribution of satellite glial cells to chemotherapy-induced neuropathic pain. *Eur J Pain* 2013; **17**: 571-80
- 132 Zhang H, Yoon SY, Zhang H, Dougherty PM. Evidence that spinal astrocytes but not microglia contribute to the pathogenesis of Paclitaxel-induced painful neuropathy. *J Pain* 2012; **13**: 293-303

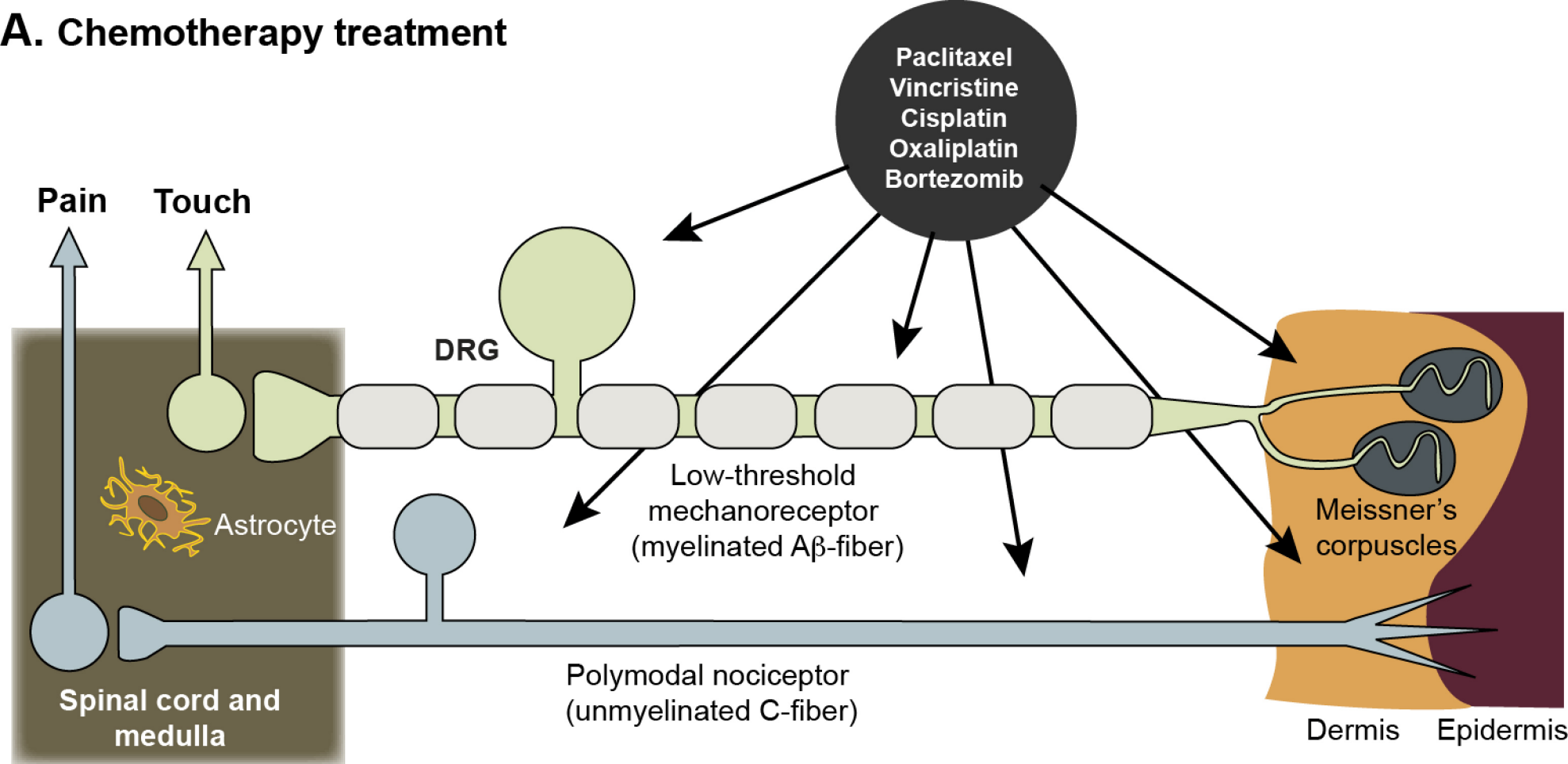


- 133 Robinson CR, Zhang H, Dougherty PM. Astrocytes, but not microglia, are activated in oxaliplatin and bortezomib-induced peripheral neuropathy in the rat. *Neuroscience* 2014; **274**: 308-17
- 134 Gao YJ, Zhang L, Samad OA, et al. JNK-induced MCP-1 production in spinal cord astrocytes contributes to central sensitization and neuropathic pain. *J Neurosci* 2009; **29**: 4096-108
- 135 Yoon SY, Robinson CR, Zhang H, Dougherty PM. Spinal astrocyte gap junctions contribute to oxaliplatin-induced mechanical hypersensitivity. *J Pain* 2013; **14**: 205-14
- 136 Robinson CR, Dougherty PM. Spinal astrocyte gap junction and glutamate transporter expression contributes to a rat model of bortezomib-induced peripheral neuropathy. *Neuroscience* 2015; **285**: 1-10
- 137 Zhang H, Dougherty PM. Enhanced excitability of primary sensory neurons and altered gene expression of neuronal ion channels in dorsal root ganglion in paclitaxel-induced peripheral neuropathy. *Anesthesiology* 2014; **120**: 1463-75
- 138 Grolleau F, Gamelin L, Boisdron-Celle M, Lapied B, Pelhate M, Gamelin E. A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels. *J Neurophysiol* 2001; **85**: 2293-7
- 139 Webster RG, Brain KL, Wilson RH, Grem JL, Vincent A. Oxaliplatin induces hyperexcitability at motor and autonomic neuromuscular junctions through effects on voltage-gated sodium channels. *Brit J Pharmacol* 2005; **146**: 1027-39
- 140 Park SB, Goldstein D, Lin CS, Krishnan AV, Friedlander ML, Kiernan MC. Acute abnormalities of sensory nerve function associated with oxaliplatin-induced neurotoxicity. *J Clin Oncol* 2009; **27**: 1243-9
- 141 Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC. Oxaliplatin-induced neurotoxicity: changes in axonal excitability precede development of neuropathy. *Brain* 2009; **132**: 2712-23
- 142 Masocha W. Gene expression profile of sodium channel subunits in the anterior cingulate cortex during experimental paclitaxel-induced neuropathic pain in mice. *PeerJ* 2016; **4**: e2702
- 143 Grothey A. Clinical management of oxaliplatin-associated neurotoxicity. *Clin Colorectal Cancer* 2005; **5 Suppl 1**: S38-46
- 144 Lehty TJ, Leonard GD, Wilson RH, Grem JL, Floeter MK. Oxaliplatin-induced neurotoxicity: acute hyperexcitability and chronic neuropathy. *Muscle Nerve* 2004; **29**: 387-92
- 145 Thibault K, Calvino B, Dubacq S, et al. Cortical effect of oxaliplatin associated with sustained neuropathic pain: exacerbation of cortical activity and down-regulation of potassium channel expression in somatosensory cortex. *Pain* 2012; **153**: 1636-47
- 146 Descoeur J, Pereira V, Pizzoccaro A, et al. Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. *EMBO Mol Med* 2011; **3**: 266-78
- 147 Emery EC, Young GT, Berrocoso EM, Chen L, McNaughton PA. HCN2 ion channels play a central role in inflammatory and neuropathic pain. *Science* 2011; **333**: 1462-6
- 148 Dimitrov AG, Dimitrova NA. A possible link of oxaliplatin-induced neuropathy with potassium channel deficit. *Muscle Nerve* 2012; **45**: 403-11
- 149 Nodera H, Spieker A, Sung M, Rutkove S. Neuroprotective effects of Kv7 channel agonist, retigabine, for cisplatin-induced peripheral neuropathy. *Neurosci Lett* 2011; **505**: 223-7
- 150 Matsumoto M, Inoue M, Hald A, Xie W, Ueda H. Inhibition of paclitaxel-induced A-fiber hypersensitization by gabapentin. *J Pharmacol Exp Ther* 2006; **318**: 735-40
- 151 Xiao W, Boroujerdi A, Bennett GJ, Luo ZD. Chemotherapy-evoked painful peripheral neuropathy: analgesic effects of gabapentin and effects on expression of the alpha-2-delta type-1 calcium channel subunit. *Neuroscience* 2007; **144**: 714-20
- 152 Yilmaz E, Gold MS. Sensory neuron subpopulation-specific dysregulation of intracellular calcium in a rat model of chemotherapy-induced peripheral neuropathy. *Neuroscience* 2015; **300**: 210-8
- 153 Nagy I, Friston D, Valente JS, Torres Perez JV, Andreou AP. Pharmacology of the capsaicin receptor, transient receptor potential vanilloid type-1 ion channel. *Prog Drug Res* 2014; **68**: 39-76
- 154 Simone DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. *Pain* 1989; **38**: 99-107
- 155 Marchettini P, Simone DA, Caputi G, Ochoa JL. Pain from excitation of identified muscle nociceptors in humans. *Brain Res* 1996; **740**: 109-16
- 156 Witting N, Svensson P, Gottrup H, Arendt-Nielsen L, Jensen TS. Intramuscular and intradermal injection of capsaicin: a comparison of local and referred pain. *Pain* 2000; **84**: 407-12
- 157 Hara T, Chiba T, Abe K, et al. Effect of paclitaxel on transient receptor potential vanilloid 1 in rat dorsal root ganglion. *Pain* 2013; **154**: 882-9
- 158 Quartu M, Carozzi VA, Dorsey SG, et al. Bortezomib treatment produces nocifensive behavior and changes in the expression of TRPV1, CGRP, and substance P in the rat DRG, spinal cord, and sciatic nerve. *Biomed Res Int* 2014; **2014**: 180428
- 159 Ta LE, Bieber AJ, Carlton SM, Loprinzi CL, Low PA, Windebank AJ. Transient Receptor Potential Vanilloid 1 is essential for cisplatin-induced heat hyperalgesia in mice. *Molecular Pain* 2010; **6**
- 160 Li Y, Adamek P, Zhang H, et al. The Cancer Chemotherapeutic Paclitaxel Increases Human and Rodent Sensory Neuron Responses to TRPV1 by Activation of TLR4. *J Neurosci* 2015; **35**: 13487-500

- 161 Hohmann SW, Angioni C, Tunaru S, et al. The G2A receptor (GPR132) contributes to oxaliplatin-induced mechanical pain hypersensitivity. *Sci Rep* 2017; **7**: 446
- 162 Laursen WJ, Bagriantsev SN, Gracheva EO. TRPA1 channels: chemical and temperature sensitivity. *Curr Top Membr* 2014; **74**: 89-112
- 163 Koivisto A, Hukkanen M, Saarnilehto M, et al. Inhibiting TRPA1 ion channel reduces loss of cutaneous nerve fiber function in diabetic animals: sustained activation of the TRPA1 channel contributes to the pathogenesis of peripheral diabetic neuropathy. *Pharmacol Res* 2012; **65**: 149-58
- 164 Nassini R, Gees M, Harrison S, et al. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. *Pain* 2011; **152**: 1621-31
- 165 Zhao M, Isami K, Nakamura S, Shirakawa H, Nakagawa T, Kaneko S. Acute cold hypersensitivity characteristically induced by oxaliplatin is caused by the enhanced responsiveness of TRPA1 in mice. *Mol Pain* 2012; **8**: 55
- 166 Chen J, Kang D, Xu J, et al. Species differences and molecular determinant of TRPA1 cold sensitivity. *Nature communications* 2013; **4**: 2501
- 167 Trevisan G, Materazzi S, Fusi C, et al. Novel therapeutic strategy to prevent chemotherapy-induced persistent sensory neuropathy by TRPA1 blockade. *Cancer Res* 2013; **73**: 3120-31
- 168 Trevisan G, Benemei S, Materazzi S, et al. TRPA1 mediates trigeminal neuropathic pain in mice downstream of monocytes/macrophages and oxidative stress. *Brain* 2016; **139**: 1361-77
- 169 Peier AM, Moqrich A, Hergarden AC, et al. A TRP Channel that Senses Cold Stimuli and Menthol. *Cell* 2002; **108**: 705-15.
- 170 Proudfoot CJ, Garry EM, Cottrell DF, et al. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. *Curr Biol* 2006; **16**: 1591-605
- 171 Storey DJ, Colvin LA, Mackean MJ, Mitchell R, Fleetwood-Walker SM, Fallon MT. Reversal of dose-limiting carboplatin-induced peripheral neuropathy with TRPM8 activator, menthol, enables further effective chemotherapy delivery. *J Pain Symptom Manage* 2010; **39**: e2-4
- 172 Fallon MT, Storey DJ, Krishan A, et al. Cancer treatment-related neuropathic pain: proof of concept study with menthol-a TRPM8 agonist. *Supportive Care in Cancer* 2015; **23**: 2769-77
- 173 Janes K, Esposito E, Doyle T, et al. A3 adenosine receptor agonist prevents the development of paclitaxel-induced neuropathic pain by modulating spinal glial-restricted redox-dependent signaling pathways. *Pain* 2014; **155**: 2560-7
- 174 Thibault K, Van Steenwinckel J, Brisorgueil MJ, et al. Serotonin 5-HT<sub>2A</sub> receptor involvement and Fos expression at the spinal level in vincristine-induced neuropathy in the rat. *Pain* 2008; **140**: 305-22
- 175 Hansen N, Uceyler N, Palm F, et al. Serotonin transporter deficiency protects mice from mechanical allodynia and heat hyperalgesia in vincristine neuropathy. *Neurosci Lett* 2011; **495**: 93-7
- 176 Ghelardini C, Menicacci C, Cerretani D, Bianchi E. Spinal administration of mGluR5 antagonist prevents the onset of bortezomib induced neuropathic pain in rat. *Neuropharmacology* 2014; **86**: 294-300
- 177 Moore RA, Derry S, McQuay HJ, et al. Clinical effectiveness: an approach to clinical trial design more relevant to clinical practice, acknowledging the importance of individual differences. [Review] [40 refs]. *Pain* 2010; **149**: 173-6
- 178 Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrollment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. [Review] [62 refs]. *British journal of clinical pharmacology* 2008; **66**: 266-75
- 179 Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2012; **7**: CD008943-CD
- 180 Brundage MD, Pater JL, Zee B. Assessing the Reliability of Two Toxicity Scales: Implications for Interpreting Toxicity Data. *JNCI: Journal of the National Cancer Institute* 1993; **85**: 1138-48
- 181 Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0 : Development of a comprehensive grading system for the adverse effects of cancer treatment. *Seminars in Radiation Oncology* 2003; **13(3)**: 176-81
- 182 Cornblath DR, Chaudhry V, Carter K, et al. Total neuropathy score: validation and reliability study. *Neurology* 1999; **53(8)**: 1660-4
- 183 Merkies IS, Schmitz PI, van der Mech, FG, van Doorn PA. Psychometric evaluation of a new sensory scale in immune-mediated polyneuropathies. Inflammatory Neuropathy Cause and Treatment (INCAT) Group. *Neurology* 2000; **54(4)**: 943-9
- 184 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; **85(5)**: 365-76
- 185 Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *European Journal of Cancer* 2005; **41(8)**: 1135-9
- 186 Wolf SL, Barton DL, Qin R, et al. The relationship between numbness, tingling, and shooting/burning pain in patients with chemotherapy-induced peripheral neuropathy (CIPN) as measured by the EORTC QLQ-CIPN20 instrument, N06CA. *Supportive Care in Cancer* 2012; **20**: 625-32

187 Finnerup NB, Attal N, Haroutiunian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurology* 2015; **14**(2): 162-73

## A. Chemotherapy treatment



## B. CIPN-related alterations

### Pain Dysesthesia

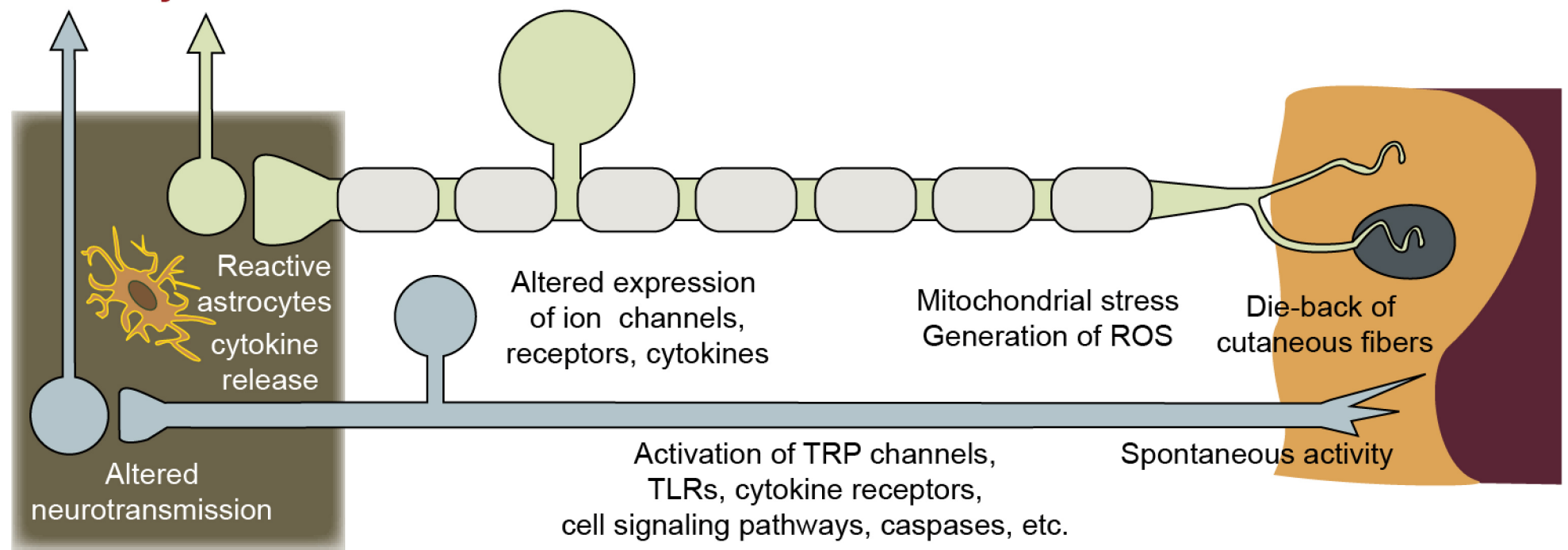


Table 1: Some of the tools used for assessing CIPN

Tool	Comments	References
National Cancer Institute-Common Toxicity Criteria (NCI-CTC)	Grade 0-3 depending on degree of sensory loss; deep tendon reflexes; parathesia	180, 181
Total Neuropathy Score clinical version (TNSc)	Includes assessment of neuropathy signs and symptoms, with limited information about pain; some quantitative sensory testing (vibration threshold, standardized monofilaments)	182
modified Inflammatory Neuropathy Cause and Treatment (INCAT) group sensory sumscore (mISS)	Includes vibration threshold, standardized monofilaments, plus 2 point discrimination	183
European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30	Not specific for CIPN, but gives a reliable measure of the impact of CIPN, and can allow comparison with other cancer populations.	184
CIPN20 quality-of-life measures	Assesses different components, including sensory, autonomic and motor symptoms;	185, 186

Table 2. Combined NNTs for agents used in treatment of neuropathic pain (based on results from <sup>187</sup>). NNT = number-needed-to-treat; CI= confidence interval; SNRI= serotonin, noradrenaline reuptake inhibitor

Drug	NNT (95% CI)	Strength of recommendation for use
SNRIs (mainly Duloxetine)	6.4 (5.2-8.4)	Strong, first line
Pregabalin	7.7 (6.5-9.4)	
Gabapentin	7.2 (5.9-9.21)	
Tri-cyclic anti-depressants	3.6 (3.0-4.4)	
Lidocaine patches 5%	Low quality evidence	Weak, second line
Capsaicin patch 8%	10.6 (7.4-19.0)	
Tramadol	4.7 (3.6-6.7)	
Strong opioids	4.3 (3.4-5.8)	Weak, third line
Botulinum toxin A	Only very small studies	Weak, third line, specialist use only